REMARKS

Status of Application

Applicants acknowledge that the request for continued examination under 37 C.F.R. § 1.114 has been entered.

Withdrawn Objections And/Or Rejections

In view of the applicant's amendment of claim 4 in Paper No.20 (19 September 2000), applicants acknowledge the withdrawal by the Examiner (page 2 of Paper No. 21 of the objections and/or rejections of claims 4, 9, 11-14 under 35 U.S.C. § 112, second paragraph, as raised in Paper No. 13 (14 October 1999).

Rejections under 35 U.S.C. § 103

The Examiner rejects claims 1, 5 and 10-14 under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al. (U.S. 5,635,599) in view of Lin for the reasons of record (pp. 3-8 of Paper No. 9, April 1999).

The Examiner maintains the position that the claimed invention is *prima facie* obvious. The Examiner argues that it would have been obvious to one skilled in the art to utilize circular permuted growth factors, DNA encoding same, methods of recombinantly producing same, and pharmaceutical compositions comprising same as taught by Pastan, and to modify the teaching by expanding it to EPO disclosed by Lin, with opening sites at 25, 27, 30, 32, 80, 82, 88, 166, or 121. The Examiner alleges that Pastan discloses that preferred opening sites are those which can tolerate amino acid

substitution, by inference from non-conserved regions in a family of related proteins.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants maintain the arguments set forth in previous amendments. The applicants have argued that the prior art merely invites further experimentation, i.e., the present rejection is based upon the repeatedly rejected improper standard of ***obvious to try***. *In re Mercier*, 185 USPQ 774 (CCPA 1975); *Ex parte Old*, 229 USPQ 196 (BPAI 1985); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *In re Geiger*, 2 USPQ2d 176 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988); *In re O'Farrell*, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

As explained in *O'Farrell* at 1681, the admonition that ***obvious to try*** is not the standard under § 103 has been directed mainly at two kinds of error:

1. Varying all parameters or trying each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical, or no direction as to which of many possible choices is likely to be successful; and

2. Exploring a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

While '599 discloses a number of general considerations for the selection of "opening sites" in a protein (last paragraph of column 8 through first paragraph of column 9) including; a) that the opening site is in a region that lacks structure; b) that the opening site is at a residue that can

be substituted or modified (ie. glycosylated); or c) that the opening site is in a conserved region amongst a related family of proteins.

However, each one these possible parameters will result in different subsets of breakpoints. '599 only teaches that in the case of IL-4 that residues 38 and 105 are potential glycosylation sites and that circular permutation at these two breakpoints results in active molecules. There is **no factual basis or experimental data** in '599 supporting the generalization that opening sites can be made at positions that are non-conserved between members of a family of related proteins or for that matter any of the other considerations for selecting breakpoints presented in '599 other than at glycosylation sites. Clearly, '599 provides numerous possible paths to take, all of which would lead one skilled in the art in different directions, and one skilled in the art is left guessing, which path to follow. '599 gives no indication as to which of the many possible directions to take.

The Examiner has previously argued that Pastan "provides guidance on selecting an opening site *depending on what is already known about the protein*" (p. 6, 1st paragraph of Paper No.17 05/03/00). Applicants respectfully submit that this type of argument is exactly the situation that *O'Farrell* has admonished as ***obvious to try***, which is not the proper legal standard under § 103. The prior art must set forth what the critical parameters are. Contrary to what is argued by the Examiner the critical parameters do not change depending on what is known about a given protein and '599 does not indicate what the critical parameters are for selecting breakpoints for EPO. Therefore, one skilled in the art is merely presented with a list of parameters from '599 to explore to determine what is critical, which constitutes undue experimentation. The

Examiner contends that '599 is a "**pioneering** patent, greatly advancing this art by its issuance" (page 4, line 5 of Paper No. 21 - emphasis added). However, there is no objective legal test that separates pioneering patents from non-pioneering patents and it is impossible for an Examiner, the United States Patent Office or the Courts to predict the future of a given technology and thereby determine the likelihood that an invention will open new vistas of innovation. Applicants agree with the Examiner that there is no need to review the prosecution history of '599. The prosecution history of '599, which constitutes part of the prior art, clearly establishes the unpredictable nature of circular permutation based on the Examiner's rejection, under 35 U.S.C. § 112, first paragraph, for lack of enablement, subsequent amendment by the patentee to dramatically narrow the scope of the claims, and from the patentee's own admission in the prosecution history. The Examiner argues the state of the art is '**quite** different' between the time of Pastan's invention and the instant invention (p. 4, 1st paragraph). However, the Examiner has failed to establish that the state of the art is '**quite** different' between the time of Pastan's invention (April 8, 1994) and the instant invention (October 25, 1996). While a handful of other proteins, which have been circularly permuted in this time period (most of which are of record) the Examiner has failed to provide factual proof regarding advances in the state of the art. At the time of the present invention there was still a great deal of unpredictability associated with circular permutation of proteins when the entirety of the state of the art is considered not an isolated snippet from '599. The burden is on the Examiner to establish the contrary. The required standard of reasonable expectation of success is based on experimental results, data, etc. present in the prior art. Thus, the reasonable expectation of success required for

a finding of obviousness requires a factual basis in the prior art, rather than mere rhetoric, as in '599. The Examiner has failed to provide any factual basis or experimental evidence in the prior art to establish that breakpoints in EPO can be made at certain positions that the Examiner has selected from a much larger set of non-conserved positions identified by homology alignment between human EPO and cynomologus monkey EPO. Applicants respectfully submit that the Examiner has failed to fulfill this burden to show a reasonable expectation of success. Therefore, the rationale of the present rejection is improper as an incorrect legal standard of reasonable expectation of success.

The Pastan disclosure fails to establish what is important in an unpredictable art area (circular permutation) but rather merely provides several different and conflicting unproven possibilities as to selecting a breakpoint and components of the fusion protein other than cytotoxins. The homology information provided by Lin does not overcome any of the shortcomings of '599. One skilled in the art is clearly presented with an obvious to try situation.

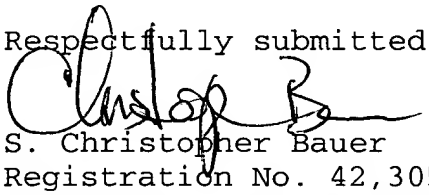
Thus, where the state of the art (such as '599 in this case) does not indicate which parameters are critical and does not provide direction as to which of many possible choices is likely to be successful, the fact that a claimed invention falls within the scope of possible combinations considered in therein does not render the invention unpatentably obvious. It is not sufficient to lead one to a forest without clear blaze marks as to the path to take. Applicants submit that the Examiner has failed to establish factual basis for a *prima facie* case of obviousness and the rejection is moot.

The Examiner rejected claims 1-4 and 6-9 under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al. (U.S. 5,635,599) in view Lin and further in view of Chaudhary and Cousens.

As presented above Pastan and Lin do not make obvious the present invention and Chaudhary and Cousens do not remedy this deficiency. Applicants submit that in view of these arguments the rejection is moot.

In view of the arguments set forth above, it is submitted that the pending claims 1-14 are in condition for allowance. Reconsideration of the rejections and objections is requested. Allowance of the pending claims at an early date is solicited. Should the Examiner find that there are unresolved issues, applicants request an interview.

Respectfully submitted,



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